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Editorial Open Access

Respiratory Complications in Acute Pancreatitis

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Editorial

Severe form of acute pancreatitis is complicated by multiple organ system dysfunctions, of which respiratory complications are the most important one. Amongst all the extra-pancreatic systemic complications, respiratory dysfunctions including acute respiratory distress syndrome (ARDS) is potentially the most serious manifestations of AP, with a mortality rate in the range of 30%-40% [1,2]. Respiratory complications occur in around three fourth of the cases of AP, ranging from mild undetected hypoxemia to fully developed ARDS [2-5]. Of the systemic complications, acute respiratory failure is a main constituent of multiple organ dysfunction syndromes (MODS), which frequently require ventilatory support, which contributes significantly to early deaths in severe cases of acute pancreatitis i.e. deaths within the first week of admission [6].

Pancreatitis develops in 3 phases of which the initial phase ensues in the first few hours and characterized by activation of intrapancreatic digestive enzyme and acinar cell damage followed by the second phase of an inflammatory reaction with acinar cell necrosis and finally, the last phase is the appearance of extrapancreatic changes where pulmonary damage occurs and ultimately leading to ARDS [7].

Various reported respiratory complications of acute severe pancreatitis include early arterial hypoxia, atelectasis, pneumonia, pleural effusion, mediastinal abscess, pulmonary infarction, elevated diaphragm, empyema, acute lung injury and finally acute respiratory distress syndrome [8,9].

The clinical presentations of respiratory complications in AP can be described in three types. Type 1 abnormalities include cases with pulmonary manifestations but without any noticeable radiological abnormalities, while type 2 has obvious radiologic changes along with hypoxemia and type 3 includes cases of fully developed ARDS [8].

Type 1 patient may have hypoxemia, tachypnea, and mild respiratory alkalosis which may present in up to two thirds of patients with AP on presentation [10]. In these patients, physical examination and chest radiographs rarely demonstrate any abnormality but arterial oxygen tensions may be lowered [11], and if severe, then may be associated with increased mortality [3]. Oxygen saturation of 92% or below is also has been considered as an independent predictor to predict the severity of acute pancreatitis [12]. The probable underlying aetiology of this hypoxia is ventilation and perfusion mismatch [13] and it is the the most important precipitating factor for ARDS during the first week of acute pancreatitis [14]. In second type of patients various radiological abnormalities may include pulmonary infiltrates or atelectasis (15%), pleural effusions (4%-17%), and pulmonary edema/ARDS (8%-50%), are the pulmonary manifestations of AP in this category and a few of these patients may require ventilatory support with significantly higher mortality and morbidity are as compared to group 1 patients [8]. Presence of radiological evidence of respiratory involvement is associated with around 15-fold increased mortality rate [6]. Currently, presence abnormal chest radiograph findings (like presence of pleural effusion and/or pulmonary parenchymal lesions) within 24 hours of hospitalisation can be considered as one of the important tests to identify subgroups of patients with more severe disease or adverse clinical outcome [15]. Presence of baseline hypoxemia (PaO_2<60 mmHg) can also be used as a marker of poor outcome as it is an indicator of underlying pulmonary consolidation and/or ARDS [4]. More than half of the patients (up to 55%) have abnormal chest radiographic findings in patients with acute pancreatitis and primarily include pleural effusion, pulmonary infiltrates, and pulmonary oedema. Pleural effusion has been observed in 4-20% of patients [15]. Pleural effusions when present, are frequently small, left sided, and are characterized by high amylase (up to 30 times of serum values), protein (>30 gm/L), and lactic acid dehydrogenase (ratio) (>0.6 serum value) levels [5]. Two main mechanisms of pleural effusion development are trans-diaphragmatic lymphatic blockage or pancreatico-pleural fistulae secondary to leak and disruption of the pancreatic duct leading to pancreatic enzymes tracking up into the mediastinum and then rupture into the pleural cavity either left side or bilaterally. In these patients, cough, dyspnea, chest pain, atelectasis, hypoxia may be observed. A correlation between the presence of pleural effusion on admission and disease severity has been well established and, in fact, it is recommended now that search for pleural effusion by ultrasound should be carried out in all patients of acute pancreatitis [16]. Atelectasis and lung consolidation in these patients is attributed to a decrease in the production of pulmonary surfactant [17] while in the lower regions of the lung; diaphragmatic impairment may be responsible for atelectasis via decreased ventilation of these regions [18]. Average timing of the development of the respiratory complications from the onset of acute pancreatitis is variable and has been reported to be around 4 days for pleural effusion, 5 days for atelectasis and 12 days for ARDS [4].

Third type of patients present with full blown ARDS which is the most perilous pulmonary complication of acute pancreatitis. About 15% to 20% of AP patients develop ARDS in due course with an associated mortality of 56% [19] while ARDS is responsible for 50%-90% of all deaths from pancreatitis [20]. These patients have severe dyspnea and extreme hypoxemia which is refractory to a high flow inspired oxygen concentration due to increased micro vascular permeability with interstitial oedema [21].

In the pathogenesis of respiratory complications of AP, Inflammatory mediators released from pancreatic injury and digestive actions of pancreatic enzymes play a key role. The role of active digestive enzymes in circulation, release of multiple pro-inflammatory cytokines, activation and migration of leukocytes/neutrophils, complement mediated injury, and platelet activating factors are primarily involved in development of these complication. A damage to the pulmonary vasculature caused by activated trypsin leads to increased endothelial permeability while the main culprit for pulmonary insufficiency and ARDS in patients of acute pancreatitis is Phospholipase A by virtue of destruction of the surfactant by phospholipase A2 [21].

Pulmonary parenchymal damage in AP is the result of a marked systemic inflammatory response and microscopically characterized by increased endothelial and epithelial barrier permeability leading to an initial exudative phase during day 1-3 with a diffuse alveolar damage, type I pneumocyte necrosis, and influx of inflammatory cells with leakage of a protein-rich exudate into the alveolar space and interstitial tissues. This is followed by a proliferative phase from days 3-7 with lung repair, type II pneumocyte hyperplasia and fibroblast proliferation. These changes cause compromise in oxygenation and gas exchange [21]. Multiple cellular elements like neutrophils, monocytes, and macrophages are recruited and activated at different phases by several cytokines, chemokines like interleukin- 8 (IL-8) and monocyte chemoattractant protein (MCP)-1, which regulate the migration and pulmonary infiltration of these cells into the interstitial tissue, where they cause injury and breakdown of the pulmonary parenchyma [22,23]. Proteases derived from polymorphonuclear neutrophils, and various pro-inflammatory mediators are also involved in pathogenesis of ALI and ARDS. Other contributing factors that promote acute pancreatitis-associated lung injury may also be found in the gut and mesenteric lymphatics [1]. Some other inflammatory mediators also play a vital role in the pathogenesis of pancreatitis associated lung injury. These mediators include proinflammatory cytokines like TNF-α and interleukins(1β, -6, and -10), platelet-activating factor (PAF), transforming growth factor-β, selectin and adhesion molecules, Free fatty acids, granulocyte-macrophage colony-stimulating factor, neuropeptide substance P, complement component C5a, fMet-leu-phe (a bacterial wall product), nitric oxide, macrophage migration inhibitor factor (MIF) and macrophage inflammatory protein-1α [8,24].

The most important aspect in the treatment of respiratory complications of acute pancreatitis is supportive care which includes replacement of fluid and electrolytes; correction of metabolic abnormalities, appropriate use of nasogastric suction and antibiotics, and parenteral nutrition along with required medical or surgical therapies for AP. Treatment of pleural effusion is by and large conservative. Most often, pleural effusions spontaneously resolve when the intra-abdominalm aetiology is resolved; however, in the face of respiratory compromise or infection or when it becomes symptomatic, it often requires thoracentesis or tube thoracostomy with other supportive treatment [8,9]. Sometimes chronic effusions require drainage of the pseudo cyst or abscess or excision of the fistulous tract [5].

In patients with atelectasis who are spontaneously breathing, an acceptable oxygenation can be achieved by application of continuous positive-airways pressure (CPAP) of between 5 and 10 cm H_20 which re-expands collapsed alveoli, increasing functional residual capacity and lung compliance, such that the work of breathing is reduced and gas exchange is improved [9].

Patients with coexistent pneumonia or empyema require respiratory support, hydration, and administration of broad spectrum antibiotics. Empyema may require transcutaneous drainage and rarely open surgical drainage under ultrasound guidance.

In patients with progressive pulmonary insufficiency or ARDS in AP, treatment remains supportive and aims to maintain adequate oxygen delivery to all organ systems. Respiratory support primarily includes application of either non-invasive mechanical ventilation and when required, endotracheal intubation with invasive mechanical ventilation. Renal support in the form of fluid and electrolyte balance and include diuretics and fluid restriction if the cardiac output and required oxygenation is maintained [9].

To conclude, there are a wide variety of respiratory complications in cases of acute pancreatitis but ARDS being the most serious one requiring substantial attention and resources. The understanding of pathophysiology of these disorders has been better understood in recent times and may provide us with novel tools for prevention and improvement in the management of these complications in near future but still the treatment remains largely empirical and supportive. Respiratory physicians must be aware of the range of disorders as these are quite commonly associated with AP and failure to identify these may lead to significant morbidity and mortality.

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